AD NUMBER

AD835281

NEW LIMITATION CHANGE

TO

Approved for public release, distribution unlimited

FROM

Distribution authorized to U.S. Gov't. agencies and their contractors; Critical Technology; NOV 1965. Other requests shall be referred to Department of the Army, Fort Detrick, Attn: Technical Releases Branch, Frederick, MD 21701.

AUTHORITY

Fort Detrick/SMUFD ltr dtd 14 Feb 1972

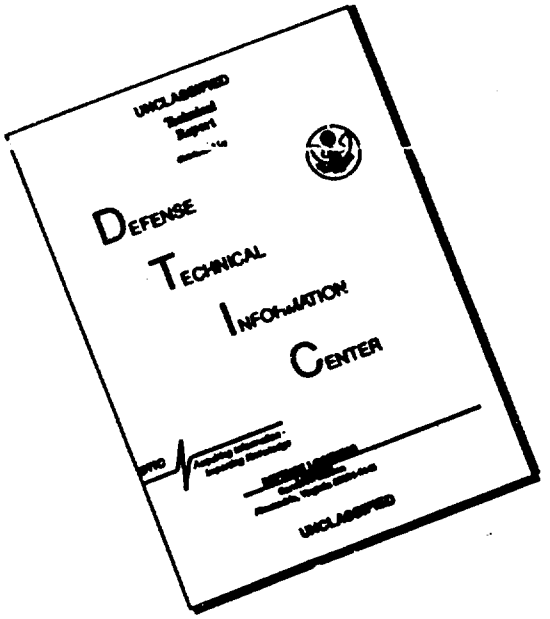
TRANSLATION NO. 1561

[redacted]

DATE: November 1965

5

DISCLAIMER NOTICE



THIS DOCUMENT IS BEST QUALITY AVAILABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF PAGES WHICH DO NOT REPRODUCE LEGIBLY.

EXPERIENCES WITH THE THERAPEUTIC USE OF DIMETHYLSULFOXIDE IN ORTHOPEDICS

(Following is the translation of pages 2-5, and 42-44 of an article by Heinz John. Translation performed by Constance L. Lust)

I. Introduction:

Dimethylsulfoxide (DMSO) is a compound which has been known for approximately 100 years. In 1867 Saytzeff (45) first synthesized the compound. Presently the compound arises primarily as a waste-product from paper production. Only in the last 10 years have numerous uses been found for this material in several of the natural sciences.

At first DMSO was used as an excellent solvent in the chemical industry (synthetics, steroid hormones). The compound came to be of special interest to biologists after it became known that proteins, especially enzymes, are soluble in DMSO and remain stable in solution (28, 31, 38, 50, 51). Soon thereafter new uses and applications were found for the compound. So by adding DMSO to the suspending medium it was found that animal and human cells, or cell components (erythrocytes, tissues, bone-marrow cells and mitochondria) were protected from damage by freezing and thawing, (1,2,13,14,15,17,21,25,29,30,34,35,36,44).

In numerous investigations it was also found that the damaging or lethal effect of x-rays on bacteria, cell-cultures and animals was reduced markedly by treatment with DMSO (3,4,9,32,46,99). Generally speaking only a very slight toxicity was noted for animals when DMSO was used orally or parenterally (10,11,15,16,19,43,47).

Based on observations with plants, it was later also shown for humans and animals that absorption of several physiological materials dissolved in DMSO penetrate the skin faster. The material speeds up passage across biological membranes (6,20,23,24,43,48).

A great deal of excitement was generated by the first results in which DMSO was used therapeutically in humans. These experiments were carried out by American authors (22,34,40). Animal experiments by Jacob's group preceded these human trials. In the animal experiment it was found that application of DMSO to 3rd degree burns in rats resulted in longer life and an increased tendency to heal (22). It was also seen that for chemical burns pain decreased more rapidly and again an increased tendency to heal. Subsequently DMSO was applied externally in cases of hematoma, contusion and muscle spasms which occurred in lab personnel. Again it was seen that pain and swelling was reduced dramatically.

movement was made easier and healing was speeded very much. The patients reported a taste of garlic, or a sulfur-like taste in their mouth. This was noted very rapidly after applying DMSO externally.

The significance of this emperical observation was at hand. According to this DMSO is apparently very rapidly absorbed through the skin, has the properties of a local anesthetic, induces a decrease in swelling and enhances healing of wounded tissue.

Immediately thereafter extensive experiments and clinical trials were done in order to develop further potential theropeutic uses of DMSO, (22, 33,39,40,41,42). The main area of use for the external application of pure DMSO proved to be conditions affecting skeletal muscles (trauma, distortions, tendonitis), acute and chronic arthritis and periarthritis of varicus origins, arthoses as well as sclerosis of the skin and the contraction-structure of Dupuytren.

On the occasion of a student-trip in the fall of 1964 to Portland, Orgon, I had the opportunity to meet Professor Jacob and his coworkers. In this way I was able to see his methods and orient myself with his results. The results were very convincing and they motivated me to begin my own studies on the theropeutic effect of DMSO.

Before DMSO could be used on humans, preliminary experiments with animals had to be done. Information was required on the speed with which the material was absorbed cutaneously, and the manner in which it distributed itself in tissues after re-absorption.

The questions to be answered were:

A) Animal trials
   1) The level of DMSO in blood of the dog and rat after percutaneous application of DMSO.
   2) The speed with which it excreted in the animal.
   3) Organ distribution of DMSO after percutaneous application in reference to time of application.
   These studies were carried out with S^{35}-labelled DMSO.

B) Clinical Uses
   1) Statistical proof of level of effectiveness and duration of effectiveness in isolated cases in various sicknesses in the area of orthopedics.
   2) Dilineation of an area of usefulness for local DMSO-therapy.
   3) Investigation of the effect of DMSO in relation to the kind of pains.
   4) Determine tolerance and side-effects of local DMSO-therapy.

II. Materials and Methods

For animal trials and clinical use highly-purified, vacuum-distilled DMSO (CH_3-SO-CH_3) was obtained from Schering A.G., Berlin. The clear, colorless liquid had according to the manufacturer; a coagulation point of 18.3°-18.4°C, boiling point 190-192°C (760mm Hg, Meth. U.S.P. XVI), density (20/4°) was 1.1, and the index of refraction N^{20}_D was 1.479.

A. Animal Trials

In the first trials the behavior of the blood-level of DMSO in the dog was studied in respect to time of external application. Male beagles were used with a body weight of 11-14 kilograms. In a second series of experiments, the distribution of radioactivity in the individual organs was studied in rats 2, 6, and 24 hours after cutaneous application of labelled DMSO.

1) Radioactivity Measurement

A liquid scintillator of 50mg 1,4-bis-2-(5-phenyl-oxazotyl)-benzene and 4g. terphenyl -(1,40diphenyl-benzene* in 1000ml toluene. A Tri-carb spectrometer, Model 314 (Packard Instr. Corp, Illinois) was used to measure radioactivity (at 5°C, 1080 volts). Pulse height spectrum was set at 500v-100v.

Background for S^{35} was 25 cpm in this system. Aliquots of the preparation were burned in O_2 -air in a gas tight system. The S^{35} was collected as sulfuric acid in 20ml cold methanolic ethanolamine (30ml vacuum distilled ethanolamine in 250ml methanol). Five ml of this solution was then added to 15ml of the scintillator. The efficiency for S^{35} was 71% of theory, after combustion 35± 0.8%.

V. Conclusion

1) In the first part of this report the percutaneous absorption of S^{35}-labelled DMSO was studied in dogs. DMSO was very quickly absorbed after local application. The blood level reached a maximum in 20 minutes and remains constant at this level for 3-4 hours. Within 24 hours 35% of the total amount applied appeared in the urine.

2) In experiments with rats it was similarly proved that the material is rapidly absorbed and high blood-levels remain for several hours.

3) The distribution of DMSO in organs -as measured by S^{35}-label- after cutaneous absorption showed high accumulation of the activity in the skelatal muscle, and in the inner organ in the liver.

4) In the second part of the work are described experiences obtained from applying DMSO locally to 308 patients in an orthopedic-private practice. 100 cases of acute and chronic periarthritis were treated; 83 cases of arthrosis of the knee, 30 patients with HWS-Syndrome, as well as 95 patients with various other acute and chronic illnesses of the muscles and skelatel systems. Single doses of 5-10 ml DMSO were applied daily. With acute cases (periarthritis) 2-3 applications daily were sometimes used during the first week of treatment.

5) The clinical effect of a single treatment in 83 patients with various diseases was classified numerically according to effectiveness and length of effect. This was statistically compared. From this a clear-cut result was obtained for the acute joint afflictions. With these the effect was greater in magnitude and lasted longer.

6) In 16 individual cases the main effect was clearly demonstrated in contrast to other methods of treatment.

7) In total of 308 cases, 27.6% obtained total relief, 53.6% were markedly improved and in 18.8% no effect was noted.

8) In controls of clinical lab values (red and white cell count, differential count, thrombocyte count, and serum transaminase activity) a negative effect was noted after several months. Generally no side effects were noted which would have necessitated a curtailment of therapy. Also the "unpleasant" taste reported by some patients shortly after administration did not cause therapy to be stopped. The taste probably results from metabolism of DMSO.

9) The mechanism of action of the material is still largely unknown. It can only be assumed that besided the local effect (analgesic, speed up of absorption) a systemic effect also plays a part.

10) The result of this use of DMSO supports the concept that this treatment embodies a new therapeutic principle. The material may open new and splendid possibilities in a variety of fields.